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## Psychological Distress as a Risk Factor for Dementia Death<sup>†</sup>

Tom C. Russ MRCPsych<sup>1-3\*</sup>, Mark Hamer PhD<sup>4</sup>, Emmanuel Stamatakis PhD<sup>4</sup>,

John M. Starr FRCPEd<sup>1-3, 5</sup>, G. David Batty PhD<sup>3, 4</sup>

<sup>1</sup> Scottish Dementia Clinical Research Network, NHS Scotland, UK;

<sup>2</sup> Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK;

<sup>3</sup> Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh, UK;

<sup>4</sup> Department of Epidemiology and Public Health, University College, London, UK;

<sup>5</sup> NHS Lothian, UK

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## TO THE EDITOR

Current estimates suggest that neuropsychiatric disorders account for 28% of the global burden of disease.<sup>1</sup> While depression and anxiety (commonly referred to as psychological distress) have been shown to be a consequence of dementia, the converse is less clear. The possibility that psychological distress might be a risk factor for dementia has major public health implications. However longitudinal studies—which are best placed to examine this relationship—have, with some exceptions,<sup>2,3</sup> been small in scale (affecting study precision), excluded individuals under 65 years of age (limiting insights into the pre-older age origins of dementia), or have utilised clinical samples (reducing generalisability). Accordingly, we examined the role of psychological distress as a risk factor for and dementia death by pooling ten large, community-based cohort studies.

## METHODS

Participants were recruited from the Health Survey for England<sup>4</sup>, an annual general population-based cross-sectional study (with a longitudinal component) representative of household-dwelling individuals in England. Results from 1994–2004 were pooled. Participants gave informed consent; ethical approval was obtained from the London Research Ethics Council.

Psychological distress was measured during a household visit using the 12-item General Health Questionnaire (GHQ-12), a widely-utilized measure of psychological distress in population studies comprising items rating anxiety, depression, social dysfunction, and loss of confidence. Higher scores indicate greater distress. We employed a cut off score of  $\geq 4$  to denote psychological distress as validated against standardised psychiatric interviews.<sup>5</sup> Dementia was identified from death certification and coded according to the International Classification of Diseases (ICD) codes 290.0–290.4 and 294.9 (ICD-9) and F01, F03, F09 and G30 (ICD-10). Follow-up was until date of death or 1<sup>st</sup> January 2009—whichever came first.

We used Cox proportional hazards models to compute hazard ratios with accompanying 95% confidence intervals for GHQ-12 score in relation to dementia-related deaths. Study members scoring zero (no apparent distress) denoted the reference group. Models were adjusted for age, gender, occupational social class (OSC)<sup>6</sup>, parental OSC, age upon leaving full-time education, current smoking (yes/no), alcohol consumption (units per week), and existing cardiovascular disease (CVD; yes/no) and diabetes (yes/no). Analyses were conducted using PASW statistics 18.0 and R 2.13.0.

## RESULTS

The initial sample included 85,261 adults (in 1996 the GHQ-12 was not utilised). After removing individuals who declined linkage to mortality records (N= 9,325) and those with missing GHQ-12 data (N= 2,865) the analytic sample comprised 73,071 individuals (54.8% women) with a mean age of 55.9 years (SD 14.3, range 35–102). Data were missing for one or more variables in 21% (N= 15,355) of the sample. Individuals with missing data were more likely to be older, be female, belong to a manual OSC, leave school later, be a non-smoker, drink alcohol moderately and have CVD and diabetes.

Of the 10,170 deaths during follow-up, 455 had dementia coding. A higher GHQ-12 score was associated with increased risk of dementia death in an age-adjusted model (GHQ-12 score 1-3, HR= 1.44, 95% CI 1.17, 1.78; GHQ-12 score 4-12, HR= 1.74, 95% CI 1.36, 2.22;  $p$  (trend) < 0.001). Adding all remaining covariates (gender, OSC, parental OSC, age upon leaving full-time education, current smoking, alcohol consumption, and existing CVD and diabetes) led to some attenuation of effect but statistical significance at conventional levels was essentially retained (GHQ-12 score 1-3, HR= 1.27, 95% CI 1.00, 1.61; GHQ-12 score 4-12, HR= 1.56, 95% CI 1.17, 2.07;  $p$  (trend)=0.005). In figure 1 we relate seven categories of GHQ score to

dementia death in order to provide more detailed insight into the shape of the relationship.

There was evidence of a dose-response effect ( $p$  [trend]= 0.001). Excluding individuals with any missing data (N= 57,716; 361 dementia deaths) or dementia deaths within five years (N= 72,926; 310 dementia deaths)—the latter to explore reverse causality—did not affect our results.

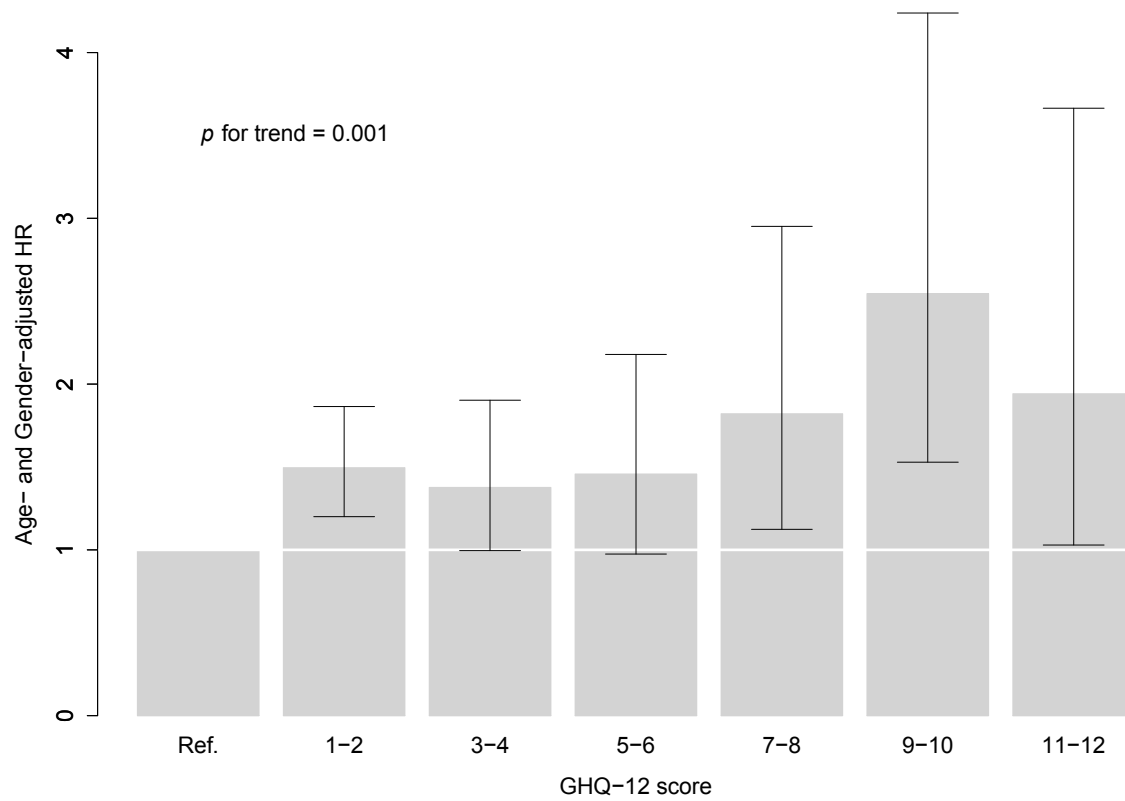
## COMMENT

We found an association between elevated psychological distress and an increased risk of dementia death in a large general population sample of apparently dementia-free adults which remained after adjustment for age, gender, OSC, education, alcohol use, smoking, and existing CVD and diabetes. Cardiovascular risk factors have been linked with dementia<sup>7</sup> but the association found here remained after controlling for them, so implicating other explanations for the gradient seen. One possibility is a toxic effect of hypercortisolaemia in depression on the hippocampus.<sup>8</sup> Further research is required to investigate whether appropriate treatment of depression reduces dementia risk.

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Figure 1. Age- and gender-adjusted hazard ratios with 95% confidence intervals for psychological distress in relation to the risk of dementia death: the Health Surveys for England



Reference = zero score on GHQ-12. Higher score indicates greater distress.